canceled claim 8. Claim 13 has been added to claim a method of treating obesity, as taught in the application as originally filed.

Claims 1, 3, and 5 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. In particular, the claim language has been adjusted to conform with accepted U.S. claim language practices. For example, parentheses were deleted, and language describing optional or alternative features of the claimed invention was clarified. Claim 6 was amended to clarify that each recited compound or its salt was claimed individually, and not necessarily in the form of a composition containing all recited compounds and salts thereof.

In claim 7, "agent" was changed to "composition" to recite the statutory term. *See* 35 U.S.C. § 101. Applicants have used "agent" and "composition" interchangeably throughout the application. *Compare, for example,* specification at page 5, lines 1-5, and page 26, line 10. Claim 7 was also modified to recite widely accepted multiply dependent claim language. Applicants note that, upon a review of their records, it appears that the fee for multiply dependent claims was not submitted yet in this application. Therefore, Applicants submit that fee with this Amendment.

Claim 8 was canceled and rewritten as claim 9. Claim 9 depends from claim 7, and merely presents the subject matter of canceled claim 8 in widely accepted claim language. Support for new claims 10 and 11, reciting forms of the amide derivatives of claim 1, find support throughout the specification and claims as originally filed, and in particular on page 8, line 24, to page 9, line 5, and page 19, lines 7-15. Claim 12, depending from claim 1 and reciting the method of treating diabetes mellitus in original

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claim 8, finds additional support in the specification generally, and in particular on pages 20-28. Claim 13 recites a method for treating obesity, and finds support in the application as filed, and in particular, in the specification on page 20, line 4, to page 21, line 11, and page 25, line 13, to page 28, line 22.

**II. Certified Copies of Priority Document**

The first page of the Office Action dated December 7, 2000, indicates that no certified copy of the priority document has been received by the Patent and Trademark Office (PTO). However, the Notification of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.494 or 1.495 mailed May 17, 2000 (a copy enclosed), indicates that a copy of the priority document *has* been received. Applicants respectfully request that the Examiner verify whether a certified copy of the priority application has been received by the PTO in this application.

**III. Restriction and Election Requirements**

The restriction requirement and species election requirement of record have been made final. *See* Office Action at page 2. While Applicants maintain their traverse of these requirements, they affirm their election with traverse of Group IV, claims 1-8 (now claims 1-7 and 9) drawn to compounds, compositions, and methods of use for Formula I wherein Z is CH, and also their election with traverse of the species of Example 7 on page 37, Example 12 on page 38, and Example 41 on page 44 of the specification. Applicants gratefully acknowledge the Examiner for refraining from restricting the claims further. *See* Office Action at page 2.

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**IV. Improper Markush Group Rejection**

Claims 1-8 have been rejected under the judicially created doctrine of improper Markush grouping, because these claims are allegedly drawn to an improper Markush group, that is, the claims allegedly lack unity of invention. *See* Office Action at page 2. The Office Action reasons that the "variables Z, X, and B, [together] with various values for other substituents are defined in such a way that they keep changing the structure/core of the compound that determines the classification/subclassification." *Id.* The Office Action has further asserted that the physical properties of the various compounds would be "tremendously altered" by the possible range of the claimed variables. In sum, the Office Action alleges an improper Markush group based on the alleged lack of unity. Applicants traverse, and disagree with the reasoning.

Among the many incorrect statements set forth in the Office Action at pages 2-3, Applicants disagree, in particular, with the statement that "[t]his feature is not inventive." *Id.* Moreover, Applicants traverse the unsupported statement that "the physical properties e.g. solubility, melting point, appearance etc. are tremendously altered with the changing of the various variable[s]," to the extent that foreseeable variation in these properties is used to support the improper Markush group rejection. Applicants request evidence on this point in accordance with MPEP § 2144.03.

Applicants respectfully request that the Examiner hold this rejection in abeyance until otherwise patentable subject matter has been identified. The Examiner kindly indicated that this rejection could be overcome by limiting the claimed invention to the elected subject matter. *See* Office Action at page 3. Applicants have traversed the

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restriction and election requirements, and if those requirements are not withdrawn, further argument now against the Markush rejection would be moot.

**V. Claim Rejections under 35 U.S.C. § 112**

Claims 1-8 have been rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking enablement for compounds and compositions wherein "heteroaryl ring = isothiazolopyridine, imidazopyridinyl, or oxobenzofuranyl, etc." Office Action at pages 3-4. Specifically, the Office Action states "while [claims 1-8 are] enabl[ed] as therapeutic agent for diabetes mellitus which comprises of the amide derivative or its salt according to claims 1-6 as an effective ingredient, [the Applicants' disclosure] does not reasonably provide enablement for compounds, compositions based on heteroaryl ring = isothiazolopyridine, imidazopyridinyl, or oxobenzofuranyl, etc." *Id.* The Office Action then analyzes several factors for determining enablement from *In re Wands* to support the rejection. *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988); *ex parte Forman,* 230 USPQ 546 (Bd. Pat. App. & Interf. 1986). Applicants respectfully traverse this rejection.

In stating the rejection, the Office Action asserts that "the claims are open-ended, and broad." This reasoning appears to suggest an indefiniteness rejection under 35 U.S.C. § 112, ¶ 2, which has not been made. Applicants traverse this assertion and ask for clarification whether the claims are rejected on this ground.

35 U.S.C. § 112, ¶ 1 requires:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

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use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Given the statutory language, "enablement requires that the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Moreover, "[t]he key word is 'undue,' not 'experimentation.' " *Id.* (internal quotations and citations omitted). To determine whether any needed experimentation is undue, the Federal Circuit listed eight factors to consider. *See id.* Applicants believe that the full scope of their claims is enabled, and set forth their counter-analysis of those eight factors below:

**(1) The nature of the invention:** Claims 1-6 recite compounds which are amide derivatives represented by the general formula (I), and salts thereof. Claim 6 names several amide derivatives and salts thereof. Claim 7 recites a composition which comprises at least one amide derivative as claimed in one of claims 1 to 6 in a pharmaceutically acceptable carrier. Claim 9 recites the composition of claim 7, wherein the amount of amide derivative is an amount effective for the treatment of diabetes mellitus. To the extent that the disclosed invention is broader than the scope of these claims, Applicants do not mean to limit the scope of their invention by this characterization. Also, Applicants point out that the claimed invention is more than just a treatment for diabetes.

**(2) The state of the prior art:** The specification describes some background of the present invention on pages 1-3. Applicants do not concede that any of the documents mentioned therein are "prior art" with respect to their invention.

**(3) The predictability or lack thereof in the art:** The Office Action asserts that a lack of predictability as to methods for making a therapeutic agent for diabetes

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mellitus has been demonstrated. Applicants traverse and ask for evidence of that demonstration. To the extent that the Office Action is correct, and yet Applicants' disclosure addresses that lack, this speaks of the patentability of Applicants' contribution to the art.

**(4) The amount of direction or guidance present, and**

**(5) The presence or absence of working examples:** The Office Action asserts: "There are no doses present for a method of preparing a therapeutic agent for diabetes mellitus." Office Action at page 5. Applicants disagree, and point to the dosage, adjuvant, and administration information on pages 26-28, among other places in the specification. The dose is "around 0.01 mg/kg to 100 mg/kg per day for adults in the case of oral administration, and that is administered at a time or by dividing into 2 to 4 times a day." Specification at page 26, lines 20-23. If the dose is given intravenously, the dosage changes to "around 0.001 mg/kg to 10 mg/kg per day for adults." *Id.*, at page 26, line 24, to page 27, line 1.

The Office Action continues: "Such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities." Office Action at page 5. To the contrary, some of many potential utilities are listed in the specification on pages 20-23, and operability is demonstrated in the specification on pages 23-26. Furthermore, if one of ordinary skill in the art sought to determine the efficacy of an amide derivative of general formula (I), that skilled artisan could follow the guidance provided in the specification for performing the hypoglycemic test in kk mice detailed on pages 23-24, the glucose tolerance test in normal rats beginning on page 24, and the test for stimulating human $\beta_3$-, $\beta_2$-, and $\beta_1$- receptors found on pages 24-25.

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The compounds of the present invention were shown to have a potentiating action to insulin sensitivity *ten times* greater than those compounds disclosed in WO 95/29159. *See* specification at page 24. Not only do the inventive amide derivatives of general formula (I) work, but they work surprisingly better.

The Office Action concludes this point of analysis by stating that "[a]ll available drugs to treat diabetes mellitus could only be used in a limited way." Office Action at page 5. Applicants respectfully point out that their invention is not limited to treating diabetes mellitus. *See* specification *generally, and in particular*, pages 20-23.

Moreover, Applicants assert that the compounds are enabled *per se*: the amide derivatives represented by the general formula (I) are described, among other places, on pages 4-9. General synthesis schemes appear in the Manufacturing Methods set forth on pages 9-20. Synthetic details for specific examples of amide derivatives represented by general formula (I) are shown on pages 36-63, and pages 64-70 tabulate physico-chemical properties of one hundred and thirteen (113) amide derivatives of the present invention actually prepared according to the disclosed syntheses.

To the extent that the rejection holds that certain heteroaryl rings are not enabled, Applicants point out the following examples actually synthesized and reported in the specification: Example 6 (imidazo[2,1-b]thiazolyl), Example 41 (aminothiazolyl), Example 60 (benzyloxypyridinyl), Example 90 (benzimidazolyl), Example 104 (pyrimidinyl), among many others.

**(6) The breadth of the claims:** Applicants believe that the breadth of their claims is fully supported by the large number of diverse amide derivatives prepared and

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described in the specification, and by the numerous tests showing efficacy of the amide derivatives, as discussed above.

**(7) The quantity of experimentation:** The Office Action asserts that there is inadequate guidance, and that the amount of experimentation required of one of ordinary skill in the art to practice the invention would be undue. *See* Office Action at 5. Applicants counter by referring again to the general and specific synthetic details provided in the specification on pages 9-20 and 36-63, the utilities listed on page 20-23, the efficacy tests described on pages 23-26, and the dosage and formulation information found on pages 26-28. To the extent that any experimentation would be needed, Applicants contend that it would be routine and not undue.

**(8) Level of skill of those in the art:** While the Office Action did not address this final *Wands* factor, it is accepted that those in the pharmaceutical, medical, and related arts possess a high level of skill.

In sum, Applicants respectfully contend that one of ordinary skill in the art finds copious enabling disclosure in the specification, and practicing the claimed invention does not require undue experimentation. Applicants therefore request that this rejection be withdrawn.

**VI. Claim Rejections under 35 U.S.C. § 102**

Claims 1-8 have been rejected under 35 U.S.C. § 102(a) without elaboration over JP 10-218861. *See* Office Action at page 6. Applicants traverse this rejection, for the reason, among many, that this Japanese document is not applicable as prior art by virtue of its publication date.

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Japanese application JP 10-218861 was published on August 18, 1998. Applicants filed their priority application on October 17, 1997. Therefore, Applicants respectfully request that this rejection be withdrawn.

Applicants perfect their claim for priority in accordance with 37 C.F.R. § 1.55(a) by submitting, a verified English translation of their priority document with this Amendment. Upon perfection of Applicants' priority date, this rejection should be withdrawn.

**VII. Claim Rejections under 35 U.S.C. § 103**

Claims 1-8 have been rejected as allegedly unpatentable over Schromm et al. (DE 3743265) in view of Toshiyuki et al. (Chem. Pharm. Bull. 39(10) 2581-2589 (1991)). See Office Action at page 6. The Office Action points out alleged structural similarities between the compounds disclosed and the present claimed amide derivatives of general formula (I), while acknowledging structural differences between them. The disclosed use of Schromm's compounds as broncholytics allegedly motivates one with knowledge of Toshiyuki's compounds, useful as antifungals, to modify Schromm's compounds to obtain Applicants' amide derivatives. Therefore, the Office Action concludes, one of ordinary skill in the art would find the amide derivatives of the present invention obvious. Applicants respectfully traverse.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

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MPEP § 2143. Applicants assert that a prima facie case of obviousness has not been established here.

The Office Action finds motivation to combine one document teaching broncholytics with another document teaching antifungals. That both disclosed classes of chemicals are useful "as pharmaceuticals" is insufficient. One prevents bronchospasm, while the other kills fungus. No motivation has been offered, besides alleged structural similarity and general use in the pharmaceutical arts, to combine these molecules, to obtain either a better broncholytic or a better antifungal. Moreover, the compounds are structurally very different. Toshiyuki et al. teaches a molecule with a phenyl group just two carbon atoms away from a triazole ring at the same end of the molecule. On the other hand, Schromm et al. discloses a molecule in which a phenyl ring attaches the *opposite end* of a substantial 5- to 9-atom amino-hydrocarbon chain, far away from any possible heterocyclic groups.

No reasonable expectation of success can be found in either cited document. The molecules disclosed by Schromm et al. on the one hand are so structurally different, and in a different field of endeavor, from those taught by Toshiyuki et al., that there is no predictability in their combination. The Office Action states that "one [making this modification] would have expected still to maintain &/or find out pharmaceutical/pharmacological activity either [the] same or different than the reference '265 [Schromm et al.]." Applicants respectfully assert that this statement reflects the unpredictable nature of the proposed modification, and thus, the modification would be merely obvious to try at best. "Obvious to try" is not the legal standard to render the present claims unpatentable. *See* MPEP § 2141.

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For at least these reasons, Applicants respectfully contend that the rejection under 35 U.S.C. § 103(a) over Schromm et al. in view of Toshiyuki et al. be withdrawn.

To the extent that the rejection relies on Schromm et al. in combination with alleged common knowledge in the art or allegedly "well-known" prior art, Applicants traverse and request that support be provided in accordance with MPEP § 2144.03.

**VIII. Documents Made of Record but Not Cited**

The Office Action makes of record US 5,541,197. *See* Office Action at page 8. The Office Action also mentions Application No. 09/297,762 (now US 6,048,884) and its division, Application No. 09/514,637 (now US 6,177,454). Applicants note that both patents are assigned to the same Assignee as the present application, and submit a copy of the '884 patent in a Supplemental Information Disclosure Statement accompanying this Amendment. The '637 application is a division of the '884 patent, and so submission of the patent obviates the need to submit a copy of the division. Applicants contend that the present claims are patentable over the referenced patent and its division, at least because the present application claims an earlier priority date than the filing date of the patent. Moreover, Applicants submit US 5,223,614 to Schromm et al., since this document appears to be an English language equivalent of Schromm et al., discussed above.

Applicants believe that the claims are patentable over these documents, and reserve the right to argue that patentability should the need arise.

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## CONCLUSION

Applicants respectfully request that all rejections be withdrawn, the application be reconsidered, and the claims allowed in a timely manner.

A Petition for Extension of Time (Two Months) and fee therefor accompany this Amendment. Please grant any further extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: May 4, 2001

By: David W. Hill
David W. Hill
Reg. No. 28,220

Enclosures:

- Appendix
- Verified Translation of Priority Document

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